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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,981	07/14/2005	Michel Maillard	02-415-A1	3761

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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
MAEWALL, SNIGDHA	

ART UNIT	PAPER NUMBER
1612	

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02/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,981	MAILLARD ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6,22,23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6,22,23 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt of applicants' arguments, remarks, amended claims and IDS filed on 10/20/08 is acknowledged.

Claims 1-2, 7-8, 10, 15-19, 21 and 24 have been cancelled.

Claims, 3-5 have been amended.

Claims **3-6, 20, 22-23 and 25-30** are under prosecution.

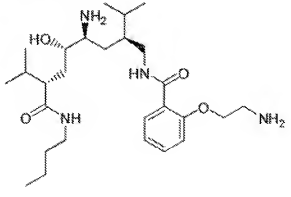
Election/Restrictions

Applicant had elected Group I, claims 3-6, 20, 22, 23, 25-30 drawn to a method of treating Alzheimer's disease to be prosecuted in the reply filed on 05/05/08. The claims are being prosecuted to the extent they read on elected species.

Applicants elected the following species in reply filed on 05/05/08.

(2S,4S,5S,7S)-N-(4-amino-7-butylcarbamoyl-5-hydroxy-2-isopropyl-8-methyl-nonyl)-2-(2-aminoethoxy)-benzamide.

This compound is shown in Example 38(b), found on page 199 of the specification, and can be represented by the following structural formula:



The rejections/objections not reiterated herein have been withdrawn in view of Applicants amendments.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 3, 5-6, 22-23 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over teachings of Amouyel et al. (Annals of New York Academy of Sciences, 903:437-441, 2000) in view of Maibaum et al. (US 5,641,778).

Amouyel et al. teach presence of renin angiotensin system components in the central nervous system. Brain angiotensin levels influence cognitive processing acquisition and recall of newly learned tasks. Increased levels of angiotensin II induce an inhibitor influence on acquisition by reducing acetylcholine release; this reduction in central cholinergic function is deleterious to cognitive functions. ACE (Angiotensin converting enzyme) inhibitors which inhibit angiotensin II synthesis will remove inhibitory influence on acetylcholine release (Page 439, 2nd paragraph, lines 1-10). Renin controls conversion of Angiotensinogen to Angiotensin I and ACE is involved in conversion of Angiotensin I to Angiotensin II (Page 438, Figure 1). As rennin inhibitors reduce the levels of angiotensin I, there will not be enough angiotensin I for ACE to act on. Thus renin inhibitors improve **cognitive function** (Page 439, 2nd paragraph, lines 1-10).

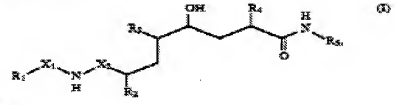
Amouyel et al. teach correlation of rennin angiotensin and cognitive performance, the reference teaches that increased rennin angiotensin is associated with decreased cognitive performance, the reference however does not disclose the claimed compound with respect to cognitive function.

Maibaum et al teach aromatically substituted omega amino alcanoic acid amides and alcanoic diamides and their use as renin inhibitors. They specifically teach compounds which are useful as **renin inhibitors** and thus useful in treatment of hypertension. Their teachings include the compound of formula I which is shown below. This compound is similar to what applicants are claiming in their claim 5 as the compound of formula (I) and compound of formula (Ia) (Claims 22 and 23) which is an obvious variant of compound of formula (I).

Maibaum et al compound of formula I is shown above

[57] **ABSTRACT**

Compounds of formula I



wherein

R_1 is a 2-R_A-3-R_B-phenyl radical, a 2-R_A-4-R_C-phenyl radical, a 2-R_A-pyridin-3-yl radical, a 3-R_A-pyridin-2-yl radical or a 1-R_D-indol-3-yl radical, wherein one of the radicals R_A and R_B is an aliphatic or heterocycloaliphatic-aliphatic radical or free or aliphatically, araliphatically or heteroaraliphatically etherified hydroxy and the other is hydrogen, an aliphatic radical or free or esterified or amidated carboxy, R_C is hydrogen, an aliphatic radical, free or aliphatically, araliphatically, heteroaraliphatically or heteroarylaliphatically etherified hydroxy or an unsubstituted or heteroaliphatically substituted amino group, and R_D is an aliphatic, araliphatic or heteroaliphatic radical, one of the radicals X_1 and X_2 is carbonyl and the other is methylene, R_2 is an aliphatic radical, R_3 is unsubstituted or aliphatically substituted amino, R_4 is an aliphatic or araliphatic radical, and R_5 is an aliphatic or cycloaliphatic-aliphatic radical or an optionally hydrogenated and/or oxo-substituted heteroaryl radical or an optionally hydrogenated and/or oxo-substituted heteroaryl or heteroaliphatyl radical bonded via a carbon atom, and the salts thereof, have renin-inhibiting properties and can be used as antihypertensive active ingredients of medicaments.

(abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the compounds disclosed by Maibaum which discloses that the compounds act as renin inhibitors. Since Amouyel teaches correlation of increased rennin angitensin with decreased cognitive performance, one skill in the art would have been motivated to utilize the compouinds disclosed by Maibum et al. in

inhibiting rennin and thus increasing cognitive performance with a reasonable expectation of success.

Response to Arguments

4. Applicant's arguments filed 10/20/08 have been fully considered but they are not persuasive.

Applicants argue that Amouyel does not teach the administration of a rennin inhibitor results in improved cognitive function. Applicant's arguments are not persuasive. The Examiner cites the following from Amouyel reference which correlates Alzheimer's disease with rennin angiotensin system proteins. The reference explicitly states that physiopathological hypothesis suggest a possible involvement of the RAS proteins in the occurrence and evolution of Alzheimer's disease.

ABSTRACT: Recent reports sustain the hypothesis of tight links between vascular and neurodegenerative diseases: associations between atherosclerosis lesions and Alzheimer's disease (AD), increased risk of AD for hypertensive subjects, decreased risk of dementia for elderly treated with hypotensive drugs, and a major impact of apolipoprotein E polymorphism, a protein of the lipid metabolism, on the occurrence of AD. All these results suggest that vascular determinants, both environmental and genetic, may predispose to or speed up dementia. As a major player of vascular homeostasis, the renin angiotensin system (RAS) proteins constitute an interesting source of candidate genes. Among these, the angiotensin I–converting enzyme gene (*ACE*), a central enzyme of the RAS, presents in its sequence a deletion (D)/insertion (I) polymorphism associated with variations of plasma ACE levels and with the risk of myocardial infarction. We explored the impact of this genetic polymorphism on the risk of cognitive impairment and of dementia in several epidemiological studies. Physiopathological hypotheses suggest a possible involvement of the RAS proteins in the occurrence and evolution of AD. Moreover, although inconsistent, several results of case-control studies tend to suggest that the *ACE* I/D genetic polymorphism may constitute a genetic susceptibility factor for dementia, reinforcing the hypothesis of a major implication of vascular risk factors in the occurrence of dementia.

Applicant argues that:

The Examiner's statement that "renin inhibitors improve cognitive function" is incorrect, and amounts to an overstatement of what Amouyel et al. actually teaches. The passages referred to by the Examiner from Amouyel only indicate that ACE inhibitor administration resulted in improved cognitive function. The reference includes no data clearly correlating inhibition of the enzyme to the improvement in cognitive function. Thus, there is no reason to believe that rennin inhibition would generate similar results. It is entirely possible that the improvement in cognitive function was the result of the compound tested operating via some other mechanism, a mechanism unrelated to the RAS.

Applicants arguments are not persuasive because Maibum discloses claimed compounds as rennin inhibitors, and since Amouyel teaches the involvement of rennin angiotensin enzymes in occurrence or evolution of Alzheimer's disease, it would have been obvious to one of ordinary skill in the art to utilize the compounds disclosed by Maibum with an expectation that the compounds would help in treating Alzheimer's disease since Maibum teaches the compounds to act as rennin inhibitors. While it is true that none of the references do specifically state that the claimed compounds treat Alzheimer's disease, the rejection is not of anticipation rather obviousness rejection based on the teachings of the prior art. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant discusses Savaskan et al.'s reference in supporting arguments. The arguments are not persuasive because the rejection is not based on Savaskan's reference. The rationale to combine the references has been discussed above.

5. Claims 4 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amouyel et al and Maibaum et al as set forth above, further in view of Rosenberg et al. (US 5,063,208) and Chen et al (US Pub 2003/0114373 A1).

The teachings of Amouyel et al and Maibaum et al have been discussed above. Both references lack the teachings of inclusion of either P-glycoprotein inhibitor or antioxidants.

Rosenberg et al (US 5,063,208) teach peptidyl aminodiol renin inhibitor compounds useful for treating hypertension congestive heart failure (Abstract). Their renin inhibitor compound is useful treating vascular diseases (Col. 46, lines 1-5). Their renin compositions contain antioxidants like sodium metabislufite (Col.46, lines 41 and 42). Their teachings include combination of their compounds with antihypertensive agents like calcium channel blockers, verapamil (Col. 47, lines 19-20, 23, 41-43) which is a suitable P-glycoprotein inhibitor as indicated by applicants (Specification, Page 35, line 1). Thus Rosenberg et al. teach renin inhibitor compositions in combination with P-glycoprotein inhibitor and antioxidant as claimed by applicants (Claims 4 and 20 respectively).

Additionally, Chen et al. (US Pub 2003/0114373 A1) teach polynucleotide encoding a calpain super family CAN-12 protease and variants (Abstract). They teach use of CAN12 for treating hypertension and neurological disorders (Page 17, paragraph 0190 11-14) including Alzheimer's disease (Page 17, paragraph 0192, lines 1-6). Their teachings include use of P-glycoprotein (PGP) antagonists in their formulations. PGP is well known for decreasing the efficacy of various drug administrations due to its ability to export intracellular levels of absorbed drug to the cell exterior (Page 159, paragraph 1328, lines 1-8). Whereas use of PGP antagonists (inhibitors) will allow drug to stay in side the cell.

Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine P-glycoprotein inhibitor as taught by Chen et al, with Maibaum et al.'s renin inhibitor to have a composition that can be retained in the cell.

Additionally based on Rosenberg et al.'s teachings of compositions containing renin inhibitor, P-glycoprotein inhibitor and antioxidants, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a composition containing Maibaum et al.'s renin inhibitor, P-glycoprotein inhibitor like verapamil and an antioxidant like sodium metabisulfite that will retain renin inhibitor inside the cell without further oxidation.

Thus It would have been obvious to one of ordinary skill in the art to use Maibaum' s renin inhibitors in combination with P-glycoprotein inhibitor and antioxidant for the treatment of Alzheimer's disease with a reasonable expectation of success since

Amouyel et al teach the involvement of renin in the conversion of angiotensin I to angiotensin II and the suggestion that renin inhibitors improve the cognitive function.

As explained above there is motivation to combine the above teachings to obtain a composition containing Maibaum et al.'s compound , P-glycoprotein inhibitor and an antioxidant for treating Alzheimer's disease and arrive at the claimed invention.

It should be noted that Applicants have not provided side by side comparison of the closes prior art with the claimed invention with scientific and technical data to show unexpected results. The rejection is maintained.

Response to Arguments

6. Applicant's arguments filed 10/20/08 have been fully considered but they are not persuasive.

Applicants argue that since the reference does not cure the deficiencies of Amouyel and Maibum et al., the rejection shall be withdrawn. Applicant's arguments are not persuasive as the rationale for combining the primary and secondary references have been cited above. The rejections will be maintained.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative or access to the automated information system, call

800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/
Examiner, Art Unit 1612
/Gollamudi S Kishore /
Primary Examiner, Art Unit 1612